REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 2-4, 6, 11, 12, 14, 19, and 23 under 35 U.S.C. § 112 (1st para.) for failing to comply with the written description requirement is respectfully traversed.

With regard to claims 2-4, 6, 19, and 23, applicants submit that the rejection under 35 U.S.C. § 112 (1st para.) for failing to comply with the written description requirement is traversed in view of the cancellation of these claims.

With regard to the written description rejection as it applies to claims 11, 12, and 14, applicants submit that a skilled scientist, having read the present application, would have understood that the inventors were in full possession of the invention as claimed.

The present invention encompasses a method of making various autoimmune disease models for any autoantigen of interest. The production of such autoimmune models requires the use of numerous knockout mice in which a gene encoding an autoantigen is functionally disrupted. To this end, the specification teaches using a Dsg3-/- mouse (a knockout for Dsg3 gene) for establishing a pemphigus vulgaris model in immunodeficient RAG2-/- mice, and teaches that the method of the present invention can be widely applicable to the preparation of model animals for other autoimmune diseases in which associated autoimmune targets have been identified. It is the position of the U.S. Patent and Trademark Office ("USPTO") that the present invention is inadequately described because the specification does not provide an adequate written description with regard to the making of the genus of autoimmune disease models other than the Dsg3-/- mouse. Applicants disagree.

Applicants submit that the gene-deficient mouse useful in the claimed invention is fully described in the present application. The donor mouse, as described in the specification, is an animal lacking an antigen for an autoimmune disease of interest, in particular, "autoimmune diseases in which associated autoimmune targets have been identified." (Pg. 5, lines 25-28). The present application teaches an exemplary autoantigen gene deficient mouse line lacking desmoglein 3 ("Dsg3"), the target antigen for pemphigus vulgaris ("PV"). The gene deficient donor mouse (Dsg3-/-) was prepared by a method well-known in the art, as described in Koch et al., *J. Cell Biol.* 137:1091-1102 (1997), which is cited at pg. 13, lines 25-27 of the present application.

"What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (*See* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, Jan. 5, 2001). Applicants submit that the production of knockout mice generally is well known in the art. Gene-deficient mice has been successfully produced many times, for many different genes, for many years. The fact that a homozygous gene-deficient mouse was conventional in the art at the time the present invention was made is evidenced by attached Exhibit 1, which contains a listing of the titles of over 500 journal articles that were retrieved in a single search of the National Institutes of Health on-line publication site using the keywords "homozygous knockout mouse." All of the references listed were published prior to March 31, 1999, the priority date of the present application. These articles teach hundreds of different knockout mice deficient in many types of genes, and demonstrate that the procedure(s) for making knockout mice were widely known and applied at the time the present invention was made. This demonstrates that the making of a loss of function gene-deficient mouse was conventional in the art by March 31, 1999. As a result, applicants submit that there was no need to furnish a detailed description of that procedure.

The USPTO also believes that it is necessary to know the genotype and phenotype of the donor mouse in order to make and use the claimed invention. In order to practice the present invention, all that needs to be known about a mouse donor is that it: (i) lacks a gene encoding the desired autoimmune antigen protein and (ii) it develops immune cells capable of producing an antibody to the desired autoimmune antigen protein. Applicants submit that the determination of these characteristics in the donor can be readily assessed by one skilled in the art. For example, the assessment of the genotype of a potential donor animal requires nothing more than the carrying out of a routine procedure, such as PCR or a Southern blot, to determine if the gene of interest is present or absent in the potential donor animal. As to the phenotype of the donor animal, all that is needed is a showing that the donor is incapable of expressing the antigen protein. This can be ascertained by methods commonly used in the art, such as a western blot, or any of the variety of well known immunoassay techniques. Thus, applicants submit that determining the genotype and phenotype of the donor is required only in a very limited sense, which is well within the knowledge and ability of one of ordinary skill in the art.

Contrary to the USPTO's position, the written description requirement does not require that the importance of the knockout antigen in the initiation and sustaining

mechanism of any autoimmune disease be explained. A skilled practitioner, having an interest in an autoimmune disease, will have investigated the "initiation and sustaining mechanism of an autoimmune disease" prior to setting out to use the claimed invention.

For all these reasons, the rejection of claims 2-4, 6, 11, 12, 14, 19, and 23 under 35 U.S.C. § 112 (1st para.) as failing to comply with the written description requirement is improper and should be withdrawn.

The rejection of claims 2-4, 6, 11, 12, 14, 19, and 23 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

With regard to claims 2-4, 6, 19, and 23, applicants submit that the rejection under 35 U.S.C. § 112 (1st para.) for lack of enablement is traversed in view of the cancellation of these claims.

With regard to the enablement rejection of claims 11, 12, and 14, applicants submit that a skilled scientist, having read the present application, would be fully able to make and use the claimed invention.

It is the position of the USPTO that the claimed invention is not enabled for the broad class of autoimmune antigen-deficient donor mice required in the claimed invention because: 1) the present application does not teach the common attributes or characteristics of a donor mouse of the claimed invention and 2) the present invention requires undue experimentation to prepare a suitable donor mouse for carrying out the claimed invention. Applicants disagree.

Firstly, applicants submit that the common attributes or characteristics of a donor mouse of the claimed invention are specifically taught in the present application. As described above, the requirements of the gene-deficient donor are simple, i.e, the donor is a mouse lacking the gene encoding an antigen for the desired autoimmune disease of interest, in particular, "autoimmune diseases in which associated autoimmune targets have been identified." (Pg. 5, lines 25-28). As described in applicants' previous response, several autoimmune diseases have been described in recent years, and the associated target antigens and their encoding genes identified. Furthermore, applicants submit that it would have been understood by one of skill in the art that the usefulness of the claimed invention is in no way limited to the exemplary pemphigus vulgaris model taught in the present application, but has wide applicability as a method to produce an autoimmune disease model.

With regard to "undue experimentation," applicants submit that the quantity of experimentation needed to be performed by one of skill in the art is only one factor involved

in determining whether "undue experimentation" is required to make and use the invention. Manual of Patent Examining Procedure § 2164.06. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). As evidenced by the large number of journal articles describing gene-deficient mice in Exhibit 1, the preparation of a gene-deficient animal was conventional in the art at the time the present invention was made. Thus, one skilled in the art, having the knowledge of an antigen protein associated with an autoimmune disease of interest and the gene encoding the autoimmune antigen protein, and having read the present application, could have readily made a knockout mouse for carrying out the present invention.

Based on all of the foregoing, applicants submit that the making of a suitably characterized donor mouse commensurate with the scope of the claimed invention is well within the purview of one skilled in the art without undue experimentation.

As further evidence that the present invention is fully enabled for making an autoimmune disease model other than PV, applicants submit Xiao et al., "Antineutrophil Cytoplasmic Autoantibodies Specific for Myeloperoxidase Cause Glomerulonephritis and Vasculitis in Mice," *J. Clinical Investigation* 110(7):955-963 (2002) ("Xiao") (attached hereto as Exhibit 2). Xiao discloses a mouse model of anti-neutrophil cytoplasmic autoantibodies (ANCAs)-associated glomerulonephritis and vasculitis. ANCAs are specific for antigens in the peroxidase-positive lysosomes of monocytes (Xiao at pg. 955, 1st para.). ANCAs-associated glomerulonephritis and vasculitis patients show two major antigen specificities for myeloperoxidase (MPO) and proteinase 3 ("PR3") (*Id.*). Xiao purified mouse MPO (Xiao, pg. 956, left col., 1st full para.), immunized a MPO gene knockout mouse (*Mpo*-/-) with the purified MPO plus an immunoadjuvant, and detected the anti-MPO antibodies produced in the knockout mouse (Xiao, pg. 956, left col., to top of pg. 957). Xiao then carried out adoptive transfer of the splenocytes of the immunized MPO gene knockout mouse to an immune deficient mouse (Rag2-/-) (Xiao, pg. 957, left col., 1st two full para.). The recipient mouse that received anti-MPO splenocytes developed circulating anti-MPO (ANCA) within 3 days (Xiao, pg. 957, rt. col., 1st full para. and Figure 1) and subsequently developed necrotizing and crescentic glomerulonephritis, granulomatous inflammation, and vasculitis (Xiao, pg. 957, rt. col., 2nd full para., to bottom of pg. 960, and Figures 2-8).

Xiao substantiates the sufficiency of the disclosure of the present application, because the method disclosed therein is the method taught in the present application, i.e., it is

"[a] method for producing a mouse recipient that produces an antibody reactive to an antigen protein for an autoimmune disease and/or has activated T cells reactive to the antigen protein, which comprises the steps of: (a) immunizing, with the antigen protein for the autoimmune disease, a mouse donor that (i) lacks a gene encoding the antigen protein and (ii) develops immune cells, (b) preparing immune cells from the donor, and (c) transplanting the immune cells to the recipient that (iii) is the same species as the donor, and (iv) has the same genetic background and/or is immunodeficient, thereby producing a mouse recipient that produces an antibody reactive to an antigen protein for an autoimmune disease and/or has activated T cells activation reactive to the antigen protein."

Furthermore, Xiao demonstrates that the immune reaction induced by MPO alone can induce the disease conditions of glomerulonephritis and vasculitis in the recipient mouse, although antibodies against MPO and PR3 are generated in ANCA-associated autoimmune diseases. Thus, Xiao supports the teaching of the present invention with regard to the making of an autoimmune mouse model even when the autoimmune disease involves more than one symptom or more than one protein.

Applicants note that the MPO knockout mice used by Xiao were the sixth generation progeny of a backcross mouse line originally made by Aratani et al., "Severe Impairment in Early Host Defense Against Candida albicans in Mice Deficient in Myeloperoxidase," *Infection and Immunity* 67(4):1828-1836 (1999) ("Aratani") (attached hereto as Exhibit 3). Aratani generated mice with a nonfunctional allele for MPO by targeted homologous recombination with mouse ES cells (Aratani at pg. 1828, rt. col., 1st full para.) as a model for studying pulmonary and systemic candidiasis (*Id.* at Abstract, last line). This is the same method used for the preparation of the Dsg3-/- knockout mouse of the present invention, as disclosed in the present application at pg. 13, lines 25-27 (i.e., Koch et al., *J. Cell Biol.* 137:1091-1102 (1997)), which further substantiates applicants' position that making autoimmune knockout mice useful in carrying out the present invention was well known at the time the present invention was made. In addition, applicants point out that the availability of the MPO mouse as a research tool for Xiao supports applicants' position that autoimmune knockouts are available in the art as starting materials for the present invention.

Based on the foregoing, it is clear that a skilled scientist, having read the present patent application, would know how to make and use the claimed invention.

Accordingly, the rejection of claims 2-8, 11-16, and 19-23 under 35 U.S.C. § 112 (1st para.) for lack of enablement is improper and should be withdrawn.

The rejection of claims 2-8, 11-16, and 19-23 under 35 U.S.C. § 112 (2nd para.) for indefiniteness based on the recitation of "has the same genetic background" is respectfully traversed.

With regard to claims 2-4, 6, 19, and 23, applicants submit that the rejection under 35 U.S.C. § 112 (2nd para.) for indefiniteness is traversed in view of the cancellation of these claims.

With regard to the indefiniteness rejection of claims 11, 12, and 14, applicants submit that one of ordinary skill in the art would fully understand what is meant by animals "having the same genetic background."

In particular, one skilled in the art would have understood "having the same genetic background" as used in the present application means genetically identical or closely related, so as to allow tissue transplant; immunologically compatible. Firstly, the present application teaches that it is preferable that the donor and the recipient have the "same genetic background, thereby preventing the onset of GVHD which may cause tissue destruction in the recipient." (Pg. 8, lines 2-6). One skilled in the art would have understood that GVHD (graft-versus-host disease) results when a tissue donor and the tissue recipient are not genetically identical, which gives rise to immunologic incompatibility and, thus, to GVHD. (*See, e.g.*, "Donor Compatibility Issues," Roswell Park Cancer Institute Patient Care Web site, copy attached here as Exhibit 4A, and "Donor Selection," *Cancer Medicine*, BC Becker on-line publishing, copy attached hereto as Exhibit 4B, describing genetic similarity between donor and recipient as important for immunologic compatibility, and that the risk of GVHD in allogeneic transplants increases as genetic similarity, and therefore, immunologic compatibility, decreases. As an example of the fact that the term "same genetic background" is well known in the art in relation to mouse-to-mouse cell transplants is shown, for example, in Kawakita et al., "Effect of Canarypox Virus (ALVAC)-Mediated Cytokine Expression on Murine Prostate Tumor Growth," *J. Natl Cancer Institute* 89(6):428-436 (1997) ("Kawakita") (attached hereto as Exhibit 5), which describes tumor cells and the animals injected with the cells as "having the same genetic background" (pg. 428, left col., 1st full para.). Hanabuchi et al., "Regression of Human T-Cell Leukemia Virus Type I (HTLV-I)-Associated Lymphomas in a Rat Model: Peptide-Induced T-cell Immunity," *J. Natl Cancer Institute* 93(23):1775-1783 (2001) ("Hanabuchi"), (attached hereto as Exhibit 6), similarly describes rats and a cell-line they were inoculated with as "having the same genetic background" (pg. 1775, left col., 1st full para.). Furthermore, as seen in Kawakita and Hanabuchi, recipient mice, to which

donor cells were transferred, accepted those cells without developing graft versus host disease ("GVHD") when the donor cells were from an animal having the same genetic background. Thus, one of skill in the art, having read the instant application, would understand that animals "having the same genetic background" are immunologically compatible animals, and that in such animals, GVHD would not occur in the recipient animals following a transfer of cells.

Accordingly, the rejection of claims 2-8, 11-16, and 19-23 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is improper and should be withdrawn.

The rejection of claims 2-4, 6, 19, and 21 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) for obviousness over Schloot, "Peripheral T Cell Clones from NOD Mice Specific for GAD65 Peptides: Lack of Islet Responsiveness or Diabetogenicity," *J. Autoimmunity* 9:357-363 (1996), is respectfully traversed in view of the cancellation of these claims.

The rejection of claims 2, 3, 6, and 21 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) for obviousness over Braley-Mullen et al., "Differential Requirement for Autoantibody-Producing B Cells for Induction of Lymphocytic versus Granulomatous Experimental Autoimmune Thyroiditis," *J. Immunol.* 152:307-314 (1994), is respectfully traversed in view of the cancellation of these claims.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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